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Pharmacological and non-pharmacological therapeutic interventions for the treatment of spinal cord injury-induced pain

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Spinal cord injury (SCI) is a complex neurophysiological disorder, which can result in many long-term complications including changes in mobility, bowel and bladder function, cardiovascular function, and metabolism. In addition, most individuals with SCI experience some form of chronic pain, with one-third of these individuals rating their pain as severe and unrelenting. SCI-induced chronic pain is considered to be “high impact” and broadly affects a number of outcome measures, including daily activity, physical and cognitive function, mood, sleep, and overall quality of life. The majority of SCI pain patients suffer from pain that emanates from regions located below the level of injury. This pain is often rated as the most severe and the underlying mechanisms involve injury-induced plasticity along the entire neuraxis and within the peripheral nervous system. Unfortunately, current therapies for SCI-induced chronic pain lack universal efficacy. Pharmacological treatments, such as opioids, anticonvulsants, and antidepressants, have been shown to have limited success in promoting pain relief. In addition, these treatments are accompanied by many adverse events and safety issues that compound existing functional deficits in the spinally injured, such as gastrointestinal motility and respiration. Non-pharmacological treatments are safer alternatives that can be specifically tailored to the individual and used in tandem with pharmacological therapies if needed. This review describes existing non-pharmacological therapies that have been used to treat SCI-induced pain in both preclinical models and clinical populations. These include physical (i.e., exercise, acupuncture, and hyper- or hypothermia treatments), psychological (i.e., meditation and cognitive behavioral therapy), and dietary interventions (i.e., ketogenic and anti-inflammatory diet). Findings on the effectiveness of these interventions in reducing SCI-induced pain and improving quality of life are discussed. Overall, although studies suggest non-pharmacological treatments could be beneficial

in reducing SCI-induced chronic pain, further research is needed. Additionally, because chronic pain, including SCI pain, is complex and has both emotional and physiological components, treatment should be multidisciplinary in nature and ideally tailored specifically to the patient.

KEYWORDS

psychological intervention, diet intervention, exercise intervention, neuropathic pain, visceral pain, musculoskeletal pain

Introduction

Between 249,000 and 363,000 Americans are currently living with spinal cord injury (SCI) (1), which represents a significant health care burden as this injury results in numerous long-term complications including, but not limited to, the loss of motor function, bowel and respiratory dysfunction, widespread inflammation, altered body composition and metabolic disorders (2). In addition, approximately 70% of individuals with SCI experience chronic pain (3), which significantly interferes with daily activities and negatively impacts quality of life. Current pharmacological interventions for pain management after SCI are largely ineffective, leading to individuals seeking alternative therapies. Studies have shown that 55–63% of individuals with SCI-induced chronic pain have tried non-pharmacological therapies (4, 5). These findings indicate that there is a need for translational research focused on the development of non-pharmacological therapies that reduce the incidence of SCI-induced pain and improve the quality of life of individuals with SCI.

One of the most common types of pain seen after SCI is neuropathic pain, which is caused by a lesion or disease of the somatosensory nervous system and can present at or below the level of injury. Neuropathic pain is frequently reported as the most severe type of pain in individuals with SCI (6), is often rated amongst the most significant patient complaints (7), and is resistant to current medical treatment (8). Neuropathic pain is usually described as sharp, shooting, or burning pain. The onset of at-level neuropathic pain generally occurs sooner (average 1.2 years) than below-level neuropathic pain (average 1.8 years) (6). The mechanisms underlying neuropathic pain are not fully defined, however changes in the periphery, spinal cord, and brain have all been implicated (9).

Conversely, the other most common type of pain after SCI is nociceptive pain, which is caused by actual or threatened damage to non-neuronal tissue and is due to activation of nociceptors. Nociceptive pain after SCI includes musculoskeletal and visceral pain. Musculoskeletal pain presents as tenderness to palpation of musculoskeletal structures, limitation of movement, and muscle spasticity. It has an average time of onset of 1.3 years and is usually described as a dull and aching pain, which originates from injury to bones, ligaments, muscles, and intervertebral

disk (6). During the acute phase, musculoskeletal pain is often associated with structural damage that has not yet healed while the chronic phase is related to abnormal loading of joints associated with objects such as wheelchair or crutch use or sustained abnormal postures resulting from the SCI. Shoulder and back pain are often seen in individuals with SCI caused by unusual demands placed on the upper limbs and muscle weakness or tension from limited mobility and continued sitting.

The function of visceral organs can also be impaired below the level of injury (10). Patients with SCI above thoracic level 10 (T10) often develop neurogenic bowel and bladder as secondary complications that contribute to reduced quality of life and impaired rehabilitation (11–13). In total 80% of patients with SCI exhibit some degree of bladder dysfunction (14) and 60% develop bowel dysfunction (15). These patients report the loss of bowel and bladder function as their highest priority of concern over below-level pain and locomotor impairment. The symptoms of neurogenic bowel and bladder include but are not limited to motility/micturition defects, constipation, fecal and urinary incontinence, and visceral pain (15–23). Visceral pain is defined by the perceived origin in deeper structures of the abdomen, thorax, and pelvis and is often difficult to localize. This type of pain is primarily described as dull and/or cramping (24, 25). Visceral pain has the longest time to onset of all post-SCI pain categories, beginning an average of 4.2 years after SCI (6). Though rates of visceral pain after SCI are lower than musculoskeletal or neuropathic pain, this type of pain still occurs in up to 60% of patients during their lifespan and is most often described as severe or excruciating (6). In addition to unrelenting visceral pain, neurogenic bowel can be particularly disadvantageous to patient welfare given that complications of neurogenic bowel (i.e., autonomic dysreflexia, septicemia, etc.) account for the most prevalent causes of emergency medical treatment during the chronic stage of SCI care (26–29).

Finally, nociplastic pain is a third type of chronic pain that has been recently defined as pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing activation of peripheral nociceptors. To our knowledge there are no published studies describing nociplastic pain in SCI. However, as nociplastic pain often occurs with other forms of chronic pain (30) it may contribute to the diagnosis of neuropathic or nociceptive pain in

individuals with SCI. Further work needs to be done to explore this topic.

Types of pharmacological and procedural therapies for SCI pain

SCI-induced chronic pain has both physical and emotional aspects, making it complex to treat. Additionally, multiple types of pain can present in a single individual and each type of pain can be influenced by behavior and environmental factors. Therefore, a multidisciplinary approach that incorporates a variety of therapeutic interventions may be most effective by targeting each of these domains simultaneously. Individuals with SCI often state that pharmacological treatments do not work in treating their pain and they prefer to explore non-pharmacological interventions to avoid unwanted side effects (4, 5). There is a growing body of evidence in both pre-clinical and clinical literature on the use of non-pharmacological treatments for SCI pain (discussed in the next section), however, the need for continued work in this domain is gaining more traction. Currently, pharmacological and procedural therapies are the most commonly used for the different types of SCI-induced chronic pain. Pharmacological therapies generally fall into 5 classes of drugs: non-steroidal anti-inflammatory (NSAIDs), anticonvulsants, anti-depressants, muscle relaxants, and opioids. Each drug class works through a different mechanism in treating SCI pain and all have varying side effects. Procedural therapies include surgical intervention, and electrical stimulation.

NSAIDs

NSAIDs such as Ibuprofen, Aspirin, and Naproxen are used to reduce inflammation, which is commonly increased after SCI at the site of spinal injury, at locations of secondary injuries, and systemically. Specifically, NSAIDs block cyclooxygenase, an enzyme involved in the process of converting arachidonic acid into prostaglandins (31). Prostaglandins are increased after tissue injury and contribute to inflammation through alterations in blood vessel dilation as well as increased vascular permeability which both work to induce edema (32). In addition, prostaglandins sensitize nociceptor terminals, which leads to increased neuronal firing that contributes to pain sensation (32). Side effects of long-term NSAID use include increased risk of dyspepsia, peptic ulcer disease, generalized upset stomach, bleeding problems, and renal dysfunction (33).

Anticonvulsants and antidepressants

Anticonvulsants and antidepressants have been investigated for their efficacy in treating SCI pain due to their use in

other neuropathic pain disorders (34). The most common anticonvulsants used to treat SCI pain include gabapentin, pregabalin, lamotrigine, and carbamazepine. Anticonvulsants are thought to improve pain after SCI through multiple mechanisms including suppression of abnormal neuronal excitability, increasing gamma-aminobutyric acid (GABA) inhibition, and modulating sodium and calcium channel activation (35). Side effects of anticonvulsants include dizziness, sleepiness, and nausea. Anti-depressants used after SCI include selective serotonin reuptake inhibitors (SSRIs), mixed serotonin-noradrenaline reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCA). Generally, antidepressants work by inhibiting serotonin and/or norepinephrine reuptake which reduces neuronal hyperexcitability. TCAs have been shown to block sodium channel activation, induce opioid receptor activity, and antagonize the NMDA receptor for glutamate (35). Overall, the benefit of TCAs in treating pain lies in their ability to prevent cellular activity through inhibition of excitatory ion channels, thereby reducing nociceptor signaling. The most common antidepressants administered for SCI pain are the TCAs amitriptyline or imipramine, however when studied in a randomized controlled trial there were no differences compared to placebo (bentropine mesylate) in either pain intensity or pain-related disability (36). Although TCAs seem to be more effective than other pharmacological drugs in treating SCI pain, they come with more severe side effects which include sleepiness, dizziness, dry mouth, constipation, and nausea.

Muscle relaxants

After SCI, decreased muscle movement and reduced descending inhibition of motor reflexes causes tightening of muscles and spasms, which are regularly associated with pain (37). Muscle relaxants, most commonly baclofen and tizanidine, are used to reduce the spasticity. Baclofen is an allosteric modulator of GABA receptors (38), which reduces spasticity through inhibition of alpha motor neurons in the spinal cord. Tizanidine also inhibits motor neurons by acting as an agonist of alpha 2-adrenergic receptors. Side effects of these medications include sleepiness and confusion.

Opioids

Opioids are one of the most effective treatments for acute pain and have been coined the standard of care for severe pain after trauma. Opioids are an agonist of the three major classes of opioid receptors: κ -opioid receptor (KOR), μ -OR (MOR), and δ -OR (DOR) (39). These receptors are located throughout the central and peripheral nervous systems in areas involved in the transmission and modulation of pain and when activated

traditionally result in analgesia (39). The MOR is the most common pharmacological target, such as with morphine or tramadol (40). Activation of the MOR reduces the presynaptic release of GABA (41) while tramadol blocks the reuptake of serotonin and norepinephrine and its metabolite is a MOR agonist (42). In addition, MOR activation modulates calcium and potassium channels, both of which are involved in pain processing (43, 44). Specifically, MOR activation results in the inhibition of N-type voltage gated calcium channels (45), which are located in the superficial laminae of the dorsal horn and control calcium entry into the synapse (46). Blocking these channels prevents the release of neurotransmitters including glutamate, substance P, and calcitonin gene related peptide (CGRP) (46). MOR activation also results in the opening of G-protein-coupled inward rectifying potassium channels (44). These channels are also located in the superficial laminae and opening them decreases neuronal excitability (47).

Despite their efficiency in acute pain reduction, opioids are associated with negative effects on the gastrointestinal tract including constipation, reduced motility, and nausea. Given that SCI patients develop gastrointestinal defects like constipation (48, 49), opioids will exacerbate gastrointestinal symptoms and prolong time to recovery. Long-term usage can result in significant side effects including sedation, respiratory depression, and bradycardia, as well as risk of tolerance, dependence, and abuse. Chronic opioid use has also been shown to result in opioid-induced hyperalgesia limiting the effectiveness in treating pain (50, 51). In addition, there is evidence in pre-clinical literature that use of opioids during the first week following SCI can impair locomotor recovery (8). The significant side effects, lack of long-term efficacy, and substance use disorders developed by opioid usage highlight the critical need for development of other pharmacological or non-pharmacological agents in pain management after SCI.

Surgical and procedural interventions

There are a limited number of individuals with SCI that benefit from surgical intervention for pain due to the destructive nature of surgery on already injured nervous system tissue. Surgery is used for neurological decompression, to stabilize spinal segments, and to correct spinal deformations (52). Neurological decompression can be used to relieve pressure on the spinal cord or nerves caused by herniated disc, bone fragmentation, or even carpal tunnel syndrome resulting from chronic wheelchair use. Decompression involves the removal of damaged structures that are compressing neural tissue to create space. Spinal fusion is used to stabilize spinal segments using an implantable device (e.g., rods, screws, plates) and/or arthrodesis of the joint, which includes fusion of the adjacent bones. Dorsal root entry zone (DREZ) lesioning is also used for SCI pain (53), which involves a laminectomy followed by the

administration of high voltage electrical activity and generation of microthermal lesions within the dorsal horn along the length of the exposed cord. However, DREZ is only used for patients after other more conservative interventions are not sufficient. While this procedure results in pain relief in certain instances, dorsal root avulsion has also been shown to result in neuropathic pain (54).

Electrical stimulation is also used for treatment of SCI pain. Transcutaneous electrical nerve stimulation (TENS), stimulation of specific brain regions, and epidural electrical stimulation of the spinal cord have all been used (55–57). These nerve stimulators can be minimally invasive by transcutaneous implantation of electrodes (58, 59) or a surgical approach which allows for direct implantation of spinal cord stimulators (60, 61). Even though there have been effective results in clinical trials, there are complications because of the invasive quality of spinal cord stimulation implantation. Some reported complications include, but are not limited to discomfort, nerve damage, cerebrospinal fluid leaking, and deafferentation (62).

Management of SCI pain using pharmacological and procedural treatments

It is estimated that as little as 1/3 of individuals with SCI-induced pain receive even a 50% reduction in pain from current pharmacological therapies (9). Pharmacological treatments for SCI pain differ primarily based on pain type (neuropathic, musculoskeletal, visceral) and severity. For example, first line pharmacological treatments for neuropathic pain include anticonvulsants [gabapentin and pregabalin (63)] and, less frequently, tricyclic antidepressants, although there is less evidence for their efficacy. Acetaminophen is considered first-line treatment for acute musculoskeletal pain followed by NSAIDs and may be used alongside a muscle relaxant like baclofen, when pain is accompanied by muscle spasticity (64) or corticosteroid injections to reduce inflammation. For persistent pain of all origins, a weak opioid, such as tramadol, is considered second-line treatment (9) while stronger opioids, such as morphine, are considered third-line treatment. However, long-term opioid use can paradoxically lead to increased pain and other problematic side effects such as constipation and opioid dependence or misuse (9). Opioids are one of the few pharmacological options used to treat visceral pain, yet can play a direct role in initiating constipation and cramps (48, 49). The mechanisms that initiate and maintain visceral pain after SCI remain unclear, and, with few mechanisms to target, few effective options for treatment and prevention exist. Pharmacological treatments are used to improve bowel motility (e.g., laxatives and antispasmodics) but they can have secondary side effects and, unfortunately, have no direct effect on visceral pain. Even with

the breadth of pharmacological approaches, patients' pain is not well controlled.

The most frequently used medical procedural interventions for SCI-induced pain include transcutaneous electrical nerve stimulation (TENS), spinal cord stimulation, surgical corrections/decompression, and DREZ to address neuropathic and musculoskeletal pain conditions (55, 65). Bladder function after SCI may be improved with prescribed spinal cord stimulation (alone or with activity-based training regimens) (61, 66) and sacral neuromodulation has been proposed to manage bladder pain syndrome/interstitial cystitis though most studies are not specific to SCI (67).

Catheterization is commonly used to treat micturition defects but does not address bladder pain directly and can lead to mechanical damage and introduce bacteria leading to inflammation and exacerbating pain (68).

Non-pharmacological treatments for SCI pain

Pain after SCI is a significant problem due to its prevalence and the difficulty to manage it. While pharmacological interventions can improve *acute* neuropathic and musculoskeletal SCI pain, efficacy is limited in treating acute visceral pain. Further, when any form of SCI pain becomes *chronic* it is even more difficult to treat. The use of non-pharmacological interventions to replace or compliment conventional medication-based treatment may improve patient neuropathic and musculoskeletal pain outcomes. However, there remains a paucity in the literature regarding nonpharmacological interventions specific to SCI-induced visceral pain and gastrointestinal/bladder disorders, limiting effective treatment development.

Exercise therapy for SCI pain

A growing body of research indicates that exercise can have a positive impact on chronic pain disorders, including migraine, fibromyalgia, pelvic pain disorders, and chronic low back pain (69, 70), although it is important that the exercise regimen is specifically tailored to the individual so as not to trigger or worsen their pain. Similarly, preclinical and clinical studies on exercise interventions for the treatment of SCI-induced chronic pain have found positive results. Additionally, exercise has been shown to reduce anxiety and depression (71), which is often found to be co-morbid in individuals with chronic pain, including pain associated with SCI (72–74).

Preclinical studies usually measure evoked mechanical or thermal pain-like behavior on the hindpaw or tail in spinally injured rodents. Mechanical nociception is most commonly measured using von Frey monofilaments (75) while thermal

nociception is most commonly inferred by measuring tail or paw withdrawal latencies following presentation of a noxious thermal stimulus (76, 77). In studies using exercise as a therapeutic intervention for SCI-induced pain in rodents, a running wheel or treadmill are frequently used. However, the start day, duration, and intensity of the exercise protocol varies between studies (78). Despite these differences, many studies have shown that exercise improves pain-like behavior in rodent models of SCI. Specifically, SCI-induced mechanical hypersensitivity has been shown to be improved by exercise when it is started during either the acute (79–85) or chronic phase of SCI (81, 86, 87). Similarly, studies have found that SCI-induced thermal hypersensitivity is also improved by exercise started during the acute (81, 83–85, 88) or chronic phase (81, 86, 87). For example, Dugan and Sagen (81) administered a T6 SCI to rats and started treadmill training either 5 (acute phase) or 21 (chronic phase) days post-injury. Training took place 5 times per week for 12 weeks. They found that treadmill training started at either time point was able to improve mechanical allodynia (measured with the von Frey method) and heat hyperalgesia (measured with the Hargreaves method). Interestingly, a follow up experiment with the same exercise parameters found that upon cessation of exercise, the positive effects of exercise on pain-like behaviors were maintained for 2 weeks. The same group also demonstrated that treadmill training started 4 weeks after SCI and continued for 2 years resulted in continued improvements in mechanical, heat, and cold hypersensitivity compared to non-exercised rats (87).

Like humans with SCI, spinally injured animals have deficits in locomotor ability, which can pose challenges for exercise interventions. To circumvent this, running wheels can be modified to make a continuous walking surface to prevent further injury (80) and treadmills can be used with partial weight support of the animal (83, 85, 89). In addition, the majority of the studies mentioned above use a moderate SCI model, that allows for some recovery of locomotor function over time. Exercise protocols can be adjusted based on the animal's recovery of function.

Although the studies described above demonstrate a positive effect of exercise on SCI-induced pain in rodents, it should be noted that exercise is not always effective. A few studies have shown that exercise has no effect on SCI-induced mechanical hypersensitivity (79, 90) or thermal hypersensitivity (79, 80, 82, 90). The differences in these studies could be due to differences in experimental parameters including the level of SCI, exercise start day, or the intensity and duration of exercise. For example, one group that uses a unilateral cervical SCI model found that while starting exercise (automated running wheels) during the acute period of injury improves pain behavior (80), starting during the chronic period does not (90). Another example comes from a study that found exercise (assisted treadmill stepping) worsened mechanical hypersensitivity (89) despite using the same injury severity and starting assisted treadmill stepping at

the same time post-injury as a study that found positive results of exercise on pain behavior (83). In this instance, the differences between the two studies were the intensity and duration of their exercise regimen. The study that found exercise worsened SCI-pain behavior used assisted treadmill stepping at a speed of 11 cm/s for 10 min/day and 5 days a week for 8 weeks. In contrast, the study that found benefits of exercise used assisted treadmill stepping at a speed of 2.5–3.5 cm/s for 20 min/day and 7 days a week for 2 weeks. These differences highlight the importance of tailoring exercise parameters to each individual when implementing an exercise intervention in clinical settings for SCI pain.

Clinical studies on exercise therapy for SCI-induced pain usually implement aerobic and/or resistance training. Arm ergometry is a commonly used form of aerobic exercise that has shown positive effects on SCI-induced chronic pain (91–93). This form of exercise, also referred to as an arm cycle or arm crank, enables an individual to pedal with their arms on an exercise machine. In addition to improving aerobic capacity, arm ergometry can also strengthen muscles in the chest, back, arms, and core. Norrbrink et al., studied the effect of arm ergometer use for 10 weeks in individuals with neuropathic, musculoskeletal, and/or visceral pain (91). They found that pain ratings in individuals with neuropathic pain decreased and all but 1 individual with musculoskeletal pain reported no pain at the end of the study. Only one individual in this study had visceral pain and it was unaffected by exercise, but the intensity of their neuropathic and musculoskeletal pain decreased. Similarly, Hicks et al., implemented a 9-month arm ergometry exercise program in individuals with SCI and found that participants had significantly less pain, stress, and depression as well as a greater quality of life (93). However, the authors did not specify what type of pain the participants had. A follow up study on these participants 3 months later revealed that exercise adherence and quality of life had significantly decreased while pain and stress both increased (94). These findings indicate that continued exercise is important in maintaining the positive effects on both pain and quality of life of individuals with SCI. Another study paired resistance training with arm ergometry for 3 months and found that exercised spinally injured individuals reported significantly less pain (type not specified), depression, and stress compared to non-exercisers (92).

While the effects of exercise on neurogenic bowel and visceral pain are currently unclear, it is typically prescribed for SCI patients as a form of motor rehabilitation. Body-weight-supported treadmill training has been shown to increase below-level motor reflex strengthening, neuronal regeneration, and reduced muscle atrophy (95–98). It has been suggested that neurogenic bowel symptom improvement could in parallel advance motor learning. This group showed that locomotor training in SCI patients reduced defecation time, improved voiding efficiency and pressure, and increased bladder capacity;

on the other hand, neither standing training nor general exercise influenced neurogenic bowel or neurogenic bladder symptoms (99, 100). This suggests that improvements in below level spinal reflexes may contribute to neurogenic bowel and bladder improvement more effectively than non-targeted exercise.

An interesting finding in several clinical studies is that the type of exercise, or general physical activity, is not necessarily a significant predictor of improvement in pain, stress, and anxiety after SCI. For example, an important study carried out by Lofgren and Norrbrink surveyed individuals with SCI-induced neuropathic pain to determine what therapies worked for decreasing their pain (101). Through diary entries and scientific interviews, they found that there was a significant disconnect in the treatment they were being offered for pain (usually drugs with unwanted side effects) and what actually worked to reduce their pain. One therapy described by multiple individuals that reduced their pain and improved their quality of life was physical activity. There was a range of physical activity among the participants (e.g., gardening, swimming, strength training, and high intensity exercise), indicating that it is important for physical activity as a therapy to be specifically tailored to an individual's capabilities and needs. A different study measured neuropathic pain scores before and after bouts of exercise in individuals with reported below-level neuropathic pain (102). This study was unique in that the pain questionnaires were completed in the individual's natural environment through a cell phone application, not in a laboratory setting. They found that participants reported a significant decrease in neuropathic pain following completion of at least one bout of exercise. Two participants did report higher pain scores after one of their bouts of exercise, and the authors speculate that intensity of the exercise may be a key factor in lowering pain scores and that more research needs to be done in this area to draw any definite conclusions. Finally, a third study determined that individuals with SCI that preformed the most sports activity (more than 3 times a week) had the lowest depression and anxiety scores and the highest score of vigor compared to less active individuals (103). Interestingly, the mode of sport did not significantly affect the results.

There are multiple mechanisms involved in mediating exercise-induced analgesia including activation of the endogenous opioid system, release of serotonin, and endocannabinoid signaling (104). Endogenous opioids are increased systemically following exercise (105) and opioidergic neurons are expressed in the rostral ventromedial medulla (RVM) (106), an important area of the brainstem involved in pain modulation. Additionally, exercise-induced analgesia can be at least partially reversed by administration of opioid receptor antagonist, naloxone, in both clinical (107, 108) and preclinical studies (109, 110). However, other studies have found that naloxone administration did not influence exercise-induced analgesia (111, 112), suggesting the involvement of other mechanisms. Serotonergic neurons are also located

in the RVM (106) and serotonin levels are increased in the brain and brainstem in preclinical models after swimming or treadmill running (113–115). Further, systemic depletion of serotonin using para-chlorophenylalanine methyl ester prevents exercise induced analgesia (115). Clinical (116) and pre-clinical work (117) have also shown that endocannabinoids are increased following exercise and that endocannabinoid receptors in areas of the brain involved in pain-modulation, such as the periaqueductal gray, are activated following exercise (118). Additionally, the administration of cannabinoid receptor inverse agonists was shown to prevent both resistance and aerobic exercise induced antinociception (117, 118). Neurotrophic factors are also suggested to play a role in exercise induced-analgesia. For example, a pre-clinical study demonstrated that exercise (body weight-supported treadmill training) increased tropomyosin-related kinase B (TrkB) and glutamic acid decarboxylases (key enzymes in the synthesis of the inhibitory neurotransmitter GABA) in the spinal cord (85). They found that blocking TrkB signaling inhibited exercise-induced analgesia and decreased levels of glutamic acid decarboxylases. Another group found that the glial cell-line derived neurotrophic factor (GDNF) family of ligands could play a role in exercise-induced analgesia following SCI. Specifically, they found that SCI-induced neuropathic pain was associated with decreased levels of GDNF and artemin in the spinal cord and DRG and increased sprouting of GDNF responsive afferents in the spinal cord dorsal horn. Exercise following SCI reduced pain and maintained GDNF and artemin levels as well as prevented sprouting of GDNF responsive afferents (80). Although the aforementioned mechanisms are centrally mediated, exercise can also have effects in the periphery including the reduction of widespread inflammation. Exercise is known to reduce inflammation (119) through multiple mechanisms including increasing the release of interleukin-6 (IL-6) which subsequently increases the anti-inflammatory cytokine IL-10 and also the IL-1 receptor antagonist, down regulating pro-inflammatory cytokine expression, and reducing pro-inflammatory monocytes in circulation.

Diet interventions for SCI pain

Individuals with SCI often experience chronic inflammation, which can contribute to the development of chronic pain (120). Specifically, SCI patients have increased circulating pro-inflammatory cytokines IL-1 β , IL-6, IL-2, tumor necrosis factor (TNF)- α , and interferon gamma (IFN- γ) (121, 122). Increased widespread inflammation is also known to be present in spinally injured rodents (123, 124). These pro-inflammatory cytokines are known to cause hyperalgesia and contribute to the development of chronic pain. Caloric and nutrient requirements change significantly after SCI and are often not adequately met (125), which can contribute to

chronic inflammation (126). There is limited research on dietary interventions for chronic pain after SCI, however, a few diets have started to be studied including the anti-inflammatory diet, the ketogenic diet, and the low fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) diet.

An anti-inflammatory diet, also commonly referred to as a Mediterranean diet, is high in fruits, vegetables, lean protein or plant based protein, whole grains, fiber, and healthy fats such as omega-3 fatty acids (127). Supplements with anti-inflammatory benefits are also common in an anti-inflammatory diet, including green tea, red wine, ginger, turmeric and antioxidants such as coenzyme Q10, tocopherols, and *n*-acetyl-cysteine. Certain foods are also eliminated from this diet, such as refined wheat and sugar products and hydrogenated oils. An anti-inflammatory diet has been shown to result in a widespread reduction in inflammation (128) and has reduced symptoms in other pain disorders in humans such as chronic headache, rheumatoid arthritis, inflammatory bowel disease, and osteoarthritis (129–131). Similarly, a pre-clinical study demonstrated that mice fed an anti-inflammatory diet displayed a shortened recovery time after an injection with the inflammatory solution complete Freund's adjuvant while another study showed that an anti-inflammatory diet improved chronic pain outcomes in a mouse model of early life stress (132). Finally, while there are no pre-clinical studies directly measuring the effect of an anti-inflammatory diet on neurogenic bowel/bladder and visceral pain, one study showed that the Mediterranean diet can rescue age-related motor learning in aged mice (133). Their findings suggest a mechanism by which neurogenic bowel outcomes could improve with a Mediterranean diet. Specifically, reduced large-molecule sugar intake and anti-inflammatory properties could lead to reduced gas/bloating as well as superoxide damage and systemic inflammation elimination. This could reduce visceral pain associated with SCI-induced neurogenic bowel.

The few clinical studies on the use of an anti-inflammatory diet for the treatment of SCI pain have demonstrated promising results. Allison et. al., measured neuropathic pain scores *via* the Neuropathic Pain Questionnaire and levels of circulating pro-inflammatory cytokines in participants with SCI after 12 weeks on an anti-inflammatory diet (134). They found that participants on the anti-inflammatory diet displayed significant reductions in neuropathic pain after 1 and 3 months on the diet compared to baseline assessment, while the participants in the control group displayed worse pain scores after 1 month and no change after 3 months. The treatment group also had significantly reduced pro-inflammatory cytokines at 3 months compared to baseline as well as compared to SCI participants on a control diet. An important follow up study in a subset of these participants examined the barriers and facilitators to adhering to this anti-inflammatory diet (135). They determined that the

greatest barriers to adherence were social events, expense of the diet, lack of knowledge about the diet, and lack of motivation after the study was over. The greatest facilitators included family and peer support, health benefits from the diet (i.e., reductions in pain, edema, and improvements in cognition and mobility), autonomy over meal selection, and the implementation of adherence strategies (i.e., incorporating cheat days/meals to cope with the strict diet).

A ketogenic diet consists primarily of high fat (70–80%), moderate protein (10–20%), and very low carbohydrates (5–10%). Certain foods are eliminated from this diet including those with refined and whole grains and starchy vegetables and fruits, while foods that are high in saturated and unsaturated fat make up the majority of the diet. The ketogenic diet was first used in humans to treat epilepsy and has since been studied as a therapeutic intervention for different ailments including weight loss, dementia, amyotrophic lateral sclerosis (ALS), cancers, and metabolic disorders such as insulin resistance and type 2 diabetes (136). Importantly, pre-clinical literature provides several examples of consumption of a ketogenic diet resulting in improvements in allodynia and ongoing pain (137–140). Currently, clinical studies on the use of a ketogenic diet in individuals with SCI have focused more on improving functional recovery after SCI rather than pain outcomes. Yarar-Fisher et al., conducted a pilot study on the safety and feasibility of a ketogenic diet after SCI and they found a ketogenic diet for 5 +/- 2 weeks significantly improved upper extremity motor scores and lowered levels of the pro-inflammatory marker fibrinogen (141). They did not see any significant differences in sensory outcomes (light touch or pin prick). Similar results were observed in a rat model of cervical SCI, where 12 weeks on a ketogenic diet significantly improved forelimb motor function (142). More work needs to be done to explore the use of a ketogenic diet for the treatment of pain following SCI. However, based on findings from pre-clinical studies that used a ketogenic diet in other pain models (137–140), it could prove to be a promising treatment option. A potential pitfall for prescribing this diet is that it can be challenging to maintain due to the carbohydrate restriction.

A diet that could be specifically beneficial for the treatment of SCI-induced neurogenic bowel and visceral pain, is the low FODMAP diet, which eliminates fermentable oligosaccharides, disaccharides, monosaccharides, and polyols from the diet (143). These are short-chain sugars that are not easily broken down or absorbed by the colon and are thought to play a role in inducing gas and bloating/gastrointestinal distention. The low FODMAP diet reduces intake of these sugars and has been shown to improve gastrointestinal symptoms but the direct effect(s) on visceral pain remain incompletely understood. In addition, probiotic dietary supplementation could also be beneficial in reducing SCI-induced neurogenic bowel symptoms. For example, a probiotic drink reduced the incidence of antibiotic-associated diarrhea in individuals with SCI (144). While this

study did not measure visceral pain, other studies have shown that probiotics reduce visceral pain symptom severity scores in individuals with irritable bowel syndrome as well as reduce bloating and altered bowel movements (145). Probiotics exert their beneficial effects on the bowel through their antimicrobial properties and by stabilizing bowel permeability (146).

The type of diet consumed can have a direct effect on an individual's inflammatory status (147), which can influence pain. One mechanism that both anti-inflammatory and ketogenic diets can have a positive impact on SCI pain is by reducing inflammation. As described before, an anti-inflammatory diet is high in fruits, vegetables, lean or plant based protein, whole grains, and healthy fats (127). Fruits and vegetables contain important vitamins, minerals, and antioxidants. Studies have shown that the higher the consumption of fruits and vegetables, the lower the level of inflammation and oxidative stress (148, 149). The consumption of red meat is low in this diet because it can increase inflammation (150). However, there is evidence that grass-fed vs. grain-fed beef products differ in their inflammatory properties such that consuming grain-fed beef can lead to higher inflammation levels compared to consuming grass-fed beef. Specifically, grass-fed beef contains higher omega-3 fatty acids, antioxidants such as glutathione and superoxide dismutase, and lower fat content compared to grain-fed beef (151). White meats and fish also have anti-inflammatory properties (147). In addition, some fish are high in omega-3 fatty acids, which have been shown to reduce pain (152). Other foods high in omega-3 fatty acids include flax seeds, walnuts, and soy beans, all of which also have anti-inflammatory properties (147). Whole grains are important in this diet because they have a low glycemic index. A diet including foods with a low glycemic index was shown to be more effective in reducing chronic inflammation (measured as C-reactive protein) compared to a diet including foods with high glycemic index (153). This study also demonstrated that high glycemic peaks was a contributor to increased oxidative stress. A ketogenic diet has also been shown to reduce inflammation in preclinical and clinical studies. For example, the consumption of a ketogenic diet increases circulating β -Hydroxybutyrate, which has been shown attenuate neuroinflammation in a rat model of SCI (137). Additionally, a ketogenic diet causes the body to utilize ketones instead of glucose for cellular energy, and ketone metabolism produces fewer reactive oxygen species and free radicals than glucose metabolism (154). Finally, ketone metabolism elevates adenosine (155), which is known to be anti-inflammatory (156).

Heat and cold therapy for SCI pain

Manipulation of temperature by exposure to heat and cold has been theorized to help with recovery following SCI. Most studies that report the use of heat treatment [i.e., application of heat to the site of SCI pain, or whole-body heat treatment

(hot tub or sauna)] for SCI pain are patient surveys. To our knowledge, no studies have been conducted to specifically examine the use of heat treatment for SCI pain. This is surprising given that heat is often reported as one of the top non-pharmacological treatments that individuals with SCI find is efficacious in reducing their pain (4, 157, 158). For example, Budh and Lundeberg used mailed questionnaires to determine the non-pharmacological treatments that were preferred by individuals with SCI-induced pain (4). Their results revealed that 90 of the 100 participants experienced neuropathic and/or nociceptive pain and that heat treatment was one of the most effective therapies for pain relief in this population. Specifically, 22 individuals had tried heat as a therapy for their pain and 77% reported that it was successful. In a similar patient survey by Ravenscroft et al., they found that 115 out of 146 individuals with SCI reported having pain (157). 80 of the individuals with pain reported having two or more different types of pain, but the pain types were not specified. They found that 21% of their sample population reported that heat treatment was one of the most effective interventions for pain relief. Finally, Tsai et al., identified effective non-pharmacological treatments in a population of individuals specifically with non-neuropathic SCI pain (158). They found that 190 of 391 participants reported 1 or more non-neuropathic pain area, most commonly located in the shoulders, back, knee, and hip. Heat therapy was one of the most frequently used non-pharmacological therapies (29%) and was said to be one of the most helpful treatments for overall non-neuropathic pain (80% of painful locations). Although the mechanisms underlying the effectiveness of heat in reducing SCI pain have not been studied, heat is known to improve blood flow and circulation, reduce inflammation, and decrease muscle and joint stiffness. Heat treatment reduces inflammation, in part, by increasing levels of heat shock proteins, which produce anti-inflammatory cytokines (159) and by improving circulation (160). In addition, decreasing muscle/joint stiffness is especially important in improving musculoskeletal pain, a common problem in individuals with SCI.

While heat therapy is often used after SCI-induced pain is established, cold therapy is usually administered in SCI patients during the very acute time period following SCI (161). Specifically, many studies have used therapeutic hypothermia within hours after injury using a cooling catheter placed in the femoral vein, a spinal cord cooling saddle, or applying cold saline to the spinal cord (161, 162). These studies reveal varying results but some show that hypothermia following SCI can result in functional improvement (162). Pre-clinical studies have found that hypothermia within hours of injury can improve locomotor function and decrease lesion severity (163). However, to our knowledge no clinical or pre-clinical studies have evaluated the development of pain following SCI in patients that have been exposed to therapeutic hypothermia, demonstrating a gap in knowledge.

Acupuncture and vagal nerve stimulation for SCI pain

Acupuncture is another non-pharmacological therapy used for treating chronic pain disorders. It involves stimulation of certain parts of the body (acupoints) by insertion of thin needles through the skin. A recent meta-analysis concluded that acupuncture has beneficial effects in individuals with chronic pain disorders such as migraine, osteoarthritis, and musculoskeletal disorders and that these effects persist over time (164). However, there are arguments in the literature regarding the efficacy of acupuncture (165). Nayak et al., studied the use of acupuncture in individuals with SCI-induced pain and found that approximately half ($n = 10$) of the participants showed significant improvements in pain intensity after 7.5 weeks of treatment (166). The authors suggest that the location of pain could determine whether acupuncture is effective, as the subset of participants that benefited from acupuncture had chronic pain located above the level of SCI. Acupuncture has also been shown to improve symptoms of SCI-induced neurogenic bowel (167) and bladder (168). It is hypothesized that acupuncture treatment reduces SCI pain through multiple mechanisms including reduction of inflammation through release of antioxidant factors, inhibition of neuronal apoptosis, and increasing expression of neurotrophins (169).

Acupuncture can also stimulate the vagus nerve (170), which is important in conveying information from visceral and somatic regions, is the major component of the parasympathetic nervous system, and is important in regulating inflammation (171). Electrical stimulation can also be used on the vagus nerve, and this form of stimulation has been shown to influence production of inflammatory cytokines in both pre-clinical (172) and clinical settings (173). Electrical vagal nerve stimulation was also shown to attenuate visceral pain measured using colorectal distension (174). Interestingly, individuals with SCI have reduced vagal tone, suggesting vagal nerve stimulation could be beneficial in this population. Indeed, Chen et al., used electrical vagal nerve stimulation in spinally injured rats and found that it improved functional recovery, reduced tissue damage, and reduced the release of pro-inflammatory cytokines (TNF α , IL1 β , and IL6) and increased levels of anti-inflammatory cytokine IL10 (175), however pain was not assessed.

Psychological interventions for SCI pain

Psychological factors, such as attitude, emotions, and coping strategies, can have a substantial impact on how an individual experiences pain. Chronic pain, including SCI-induced chronic pain, is often associated with mood disorders such as depression and anxiety (72–74). It is estimated that depression and anxiety are experienced in around 22% of

the SCI population (74). Further, each of these co-morbid disorders (depression, anxiety, and chronic pain) amplify the others and significantly impact quality of life (73). Psychological therapies, such as cognitive behavioral therapy, mindfulness-based interventions, and meditation have been successfully used as therapeutic interventions in other chronic pain disorders (176–179). Though the exact physiological mechanisms of these therapies are unclear, the intended purpose is to relax the individual to reduce autonomic output (i.e., heart rate variability, respiratory rate, etc.), encourage pain distraction, and to address maladaptive emotional responses to pain (180, 181). Incorporating these types of therapies into a pain management plan and creating a multidisciplinary approach has been shown to help individuals manage their chronic pain (182). A significant benefit of psychological interventions is that there are few to zero unwanted side effects.

Cognitive behavioral therapy consists of educating patients about their pain, techniques on how to cope with their pain, such as relaxation training, and how to implement these cognitive coping techniques in real-life situations (183). This form of psychological therapy has been shown to successfully reduce depression and anxiety symptoms in individuals with SCI (184–187). Several studies have examined if cognitive behavioral therapy is a useful treatment for reducing pain after SCI (186–189). Heutink et al., carried out a multicenter randomized control trial on the use of cognitive behavioral therapy for 10 weeks in individuals with SCI-induced neuropathic pain (188). They assessed pain intensity and pain-related disability as well as anxiety, depression, and life satisfaction before treatment and 3- and 6-months after the intervention started. They found that the intervention group, but not the control group, displayed a significant decrease in pain intensity and pain-related disability at the 3-month timepoint. The intervention group also displayed a decrease in anxiety and an increase in participation in activities at the 3- and 6-month timepoints compared to baseline. Importantly, the participants stated they would recommend this type of treatment program to others but suggested it be offered earlier following SCI. Burns et al., measured the influence of 10-weeks of cognitive behavioral therapy paired with either group exercise or guided relaxation in individuals with SCI-induced neuropathic pain. They found that although this treatment program did not reduce pain severity, it did help individuals cope with their pain, lessened pain interference with daily activities, and improved their sense of control (189). Many of the studies using cognitive behavioral therapy as a treatment for SCI-induced pain, anxiety, and/or depression suggest that “refresher” courses to reinforce skills learned during the treatment program are important to maintain efficacy of this treatment.

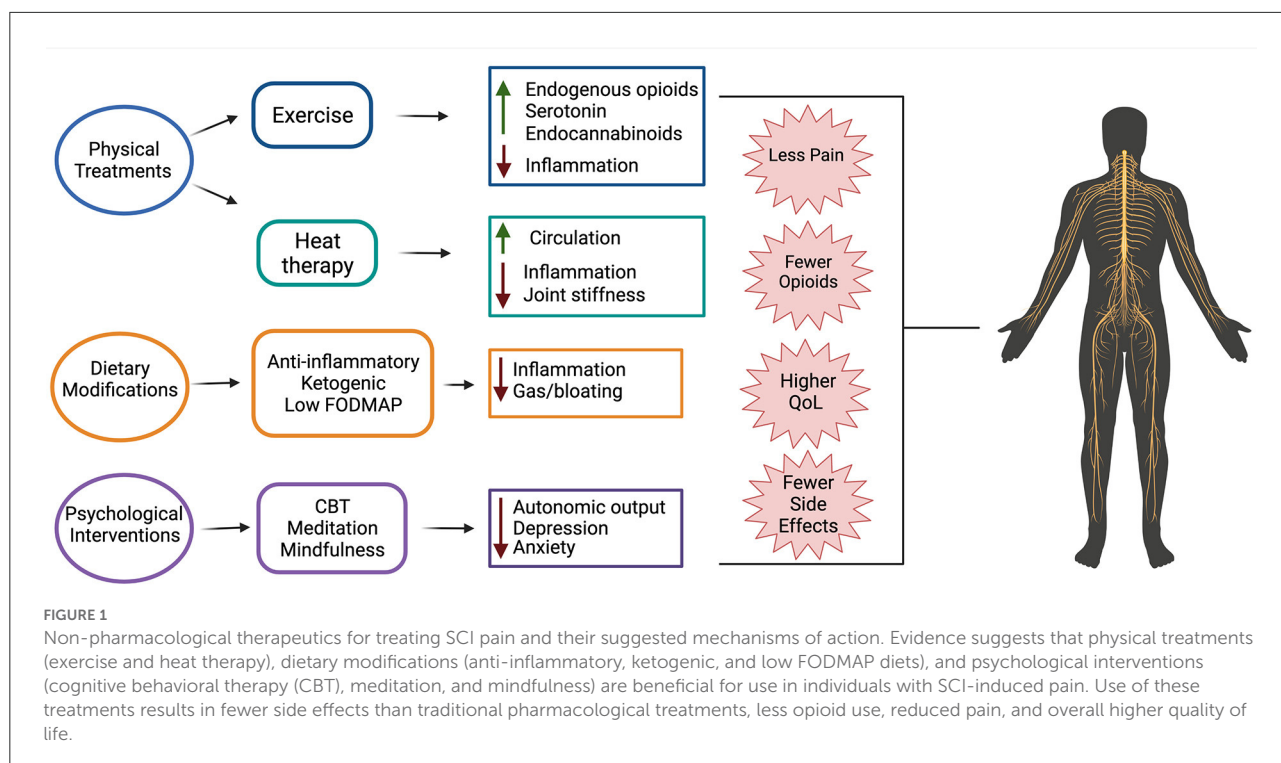
Mindfulness-based interventions are different from cognitive behavioral therapy as these interventions aim to facilitate present-moment awareness and acceptance, rather than attempting to change behavioral and psychological

responses (190). A systemic review by Streijger et al., on the use of mindfulness-based interventions in individuals with SCI pain found a variation in results on this therapy's efficacy in the 5 studies reviewed (190). One study reported a significant reduction in SCI pain, while the others reported no change. Additionally, 4/5 studies reported a significant reduction in symptoms of depression while 3/5 reported reductions in anxiety. The authors suggest that while mindfulness might not improve SCI pain, it could be used to reduce incidence of depression and anxiety in individuals with SCI-induced co-morbid pain and mood disorders. However, two recent studies using different forms of mindfulness interventions [meditation (191) and yoga (192)] in individuals with SCI, demonstrated positive outcomes on pain, anxiety, and depression. Zanca et al., used a 4-week clinical meditation and imagery program, which included mindfulness, meditation, and guided imagery in individuals with chronic nociceptive and/or neuropathic SCI pain (191). They measured pain outcomes as well as depressive symptomology and perceived stress. Their results indicated that the intervention group showed a greater decrease in depressive symptomology and worst pain intensity over the last week and a greater increase in perceived control over pain. Although their results did not reach statistical significance, the authors note that it was a pilot study and that their sample size was small. Chalageri et al., used 1 month of *raja yoga*, which is a meditation technique, and found a significant decrease in numeric pain rating, anxiety and depression, and perceived stress scale in individuals with SCI that received the *raja yoga* treatment compared to those that received conventional rehabilitation (192). Additionally, they saw a significant increase in quality-of-life scores in the intervention group.

Finally, SCI patients that have developed neurogenic bowel and/or neurogenic bladder report psychological distress, anxiety, and embarrassment about their abdominal pain, constipation, incontinence, or need for catheterization. Prescribing cognitive behavioral therapy, meditation, or yoga/exercise may improve the mental strain of neurogenic bowel and neurogenic bladder inhibiting the hyperactive autonomic nervous system as suggested by functional gastrointestinal disorders models, such as irritable bowel syndrome.

Conclusions

Chronic pain is a significant problem for individuals with SCI, in part, because current pharmacological therapies are largely ineffective. This indicates a critical need for establishment of more efficacious therapies that can be used in lieu of or in combination with current drugs. Non-pharmacological therapies are often used by individuals with SCI pain that do not find relief from traditional pharmacological therapies. These therapies are appealing



because they exert whole body effects, thereby targeting multiple mechanisms that contribute to SCI-induced pain (Figure 1). Non-pharmacological therapies are also generally safe to use and do not have negative off target effects that many pharmacological therapies do.

While many of these non-pharmacological therapies show promise in treating SCI-induced musculoskeletal or neuropathic pain, this review highlights a primary knowledge gap in the research on neurogenic bowel and bladder after SCI. These patients develop severe and unrelenting chronic abdominal pain along with bowel and bladder dysfunction. There is a critically important need to develop effective treatment options for these patients, though the complexity of these symptoms remains a barrier to effective treatment development. The few available non-pharmacological interventions suggested by this review and previous literature show promise yet are widely understudied. Each intervention appears to minimally rescue some but not all SCI-induced neurogenic bowel and neurogenic bladder symptoms, suggesting the need for a patient-specific multidisciplinary technique to cover all symptoms.

In addition, it should be noted that the majority of pre-clinical studies on SCI-induced pain have been carried out in female rodents. This is largely due to the fact that bladder expression after SCI is easier in female rodents, which results in fewer post-surgical complications (193). However, sex differences exist in many physiological processes, including

pain and inflammation (194). This caveat should be taken into consideration when designing both pre-clinical and clinical studies examining the effects of therapies on SCI-induced pain.

In conclusion, although this review describes evidence of the beneficial effects of non-pharmacological therapies, these therapies are not always successful in all individuals with SCI pain. This highlights a critical need for development of precision pain treatment that matches a patient’s pain phenotype (e.g., type of pain, severity, location) with a specific treatment strategy, which could include both pharmacologic and non-pharmacologic therapies to achieve the greatest benefit.

Author contributions

OE and AW contributed to literature review, drafting, and revision of the manuscript. EY and KB contributed to integration of reviewed literature, drafting, and revision of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships

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